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Diagnostic Pitfalls, Creatine Supplementation, Physical Activity, and Kidney Function Assessment in Non-Dialysis Chronic Kidney Disease: A Narrative Review

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Abstract

Creatine supplementation is widely used by physically active people. In patients with non dialysis chronic kidney disease, it may complicate laboratory assessment of kidney function because serum creatinine reflects both glomerular filtration and creatinine generation. Creatine intake, muscle mass, diet, and physical activity may influence serum creatinine independently of true glomerular filtration rate. This narrative review discusses interpretation of kidney function markers in patients with non dialysis chronic kidney disease who use creatine supplementation, especially in the context of physical activity or resistance training. Creatine may increase serum creatinine without a parallel reduction in true glomerular filtration rate. Creatinine based equations may translate a non filtration related creatinine rise into a lower estimated glomerular filtration rate. Physical activity may add complexity because intense exercise, muscle injury, dehydration, or exertional rhabdomyolysis may also affect creatinine, creatine kinase, and kidney function markers. Supplement history and recent training load should be interpreted together with cystatin C, albuminuria, urinary sediment, biochemical abnormalities, and clinical status. Increased serum creatinine should be treated as a diagnostic ambiguity rather than automatically classified as kidney deterioration or benign artefact. Worsening cystatin C based estimated glomerular filtration rate, increasing albuminuria, active urinary sediment, biochemical abnormalities, oliguria, edema, hypertension, or signs of exercise related muscle injury should prompt evaluation for true kidney function deterioration.

Keywords:
creatine supplementation; chronic kidney disease; creatinine; estimated glomerular filtration rate; cystatin C; diagnostic pitfall; kidney function biomarkers; physical activity; non-dialysis CKD;

1. Introduction and purpose

Creatine is widely used as a dietary supplement, mainly by individuals performing resistance training and high-intensity exercise [1,2]. Its physiological function is related to the creatine–phosphocreatine system, which supports rapid regeneration of adenosine triphosphate during short periods of increased energy demand [3]. Although creatine is most commonly associated with sports performance, recent literature has also discussed its potential role in aging, muscle wasting, neurological conditions, and clinical nutrition [2–4]. Kidney-related concerns about creatine supplementation are partly based on the biochemical relationship between creatine and creatinine [5,6]. Creatine and phosphocreatine undergo spontaneous, non-enzymatic conversion to creatinine [3]. Creatinine is then eliminated mainly by the kidneys [7,8]. As a result, creatine supplementation may increase serum creatinine in some individuals through increased creatinine generation, even when true glomerular filtration rate remains unchanged [1,5,6]. Serum creatinine is commonly used as a marker of kidney function, but it is not a direct measure of GFR. Its concentration reflects the balance between creatinine generation and renal elimination. A higher creatinine concentration may therefore result from reduced filtration, increased creatinine generation, or both [7,8]. Creatinine-based estimated glomerular filtration rate cannot identify which of these mechanisms caused the change; it converts the measured creatinine value into an estimated GFR according to the equation used [8,9]. This issue has particular relevance in CKD. In patients with established CKD, a creatinine increase may alter GFR category, influence medication dosing, affect referral decisions, or be interpreted as progression of kidney disease [7,10]. The clinical meaning of a creatinine increase is therefore different in patients with CKD than in individuals without known kidney disease, because eGFR-based thresholds are directly embedded in CKD classification, monitoring, and clinical decision-making [7,10]. The present review focuses primarily on non-dialysis CKD, because creatinine-based eGFR remains central to disease staging, monitoring, medication dosing, referral decisions, and assessment of progression before dialysis initiation. Patients receiving maintenance dialysis are not the main target population of the proposed framework, because serum creatinine and eGFR have different clinical roles after dialysis initiation. Previous systematic reviews and narrative reviews have evaluated the relationship between creatine supplementation and kidney function [1,5,6,11]. Most available data come from healthy or mixed populations and generally do not show clinically significant GFR decline during recommended creatine supplementation [1,5,6]. These findings cannot be directly applied to all CKD patients, because CKD patients differ in baseline nephron reserve, comorbidity burden, medication exposure, and susceptibility to acute kidney injury [7,10,12]. The relevant clinical question in CKD is therefore not limited to whether creatine is nephrotoxic [5,6,11]. A more specific question is how to interpret serum creatinine and eGFRcr when a non-dialysis CKD patient uses creatine supplementation [7,8]. Although creatine-related creatinine elevation and limitations of creatinine-based eGFR have been described separately, their combined diagnostic implications in patients with established CKD remain insufficiently synthesized in a practical clinical framework [7,8,11]. Two errors are possible. A creatine-related creatinine increase may be misclassified as CKD progression [5–7]. Conversely, true deterioration of kidney function may be incorrectly attributed to creatine supplementation [7,10]. The aim of this narrative review is to discuss interpretation of kidney function markers in physically active patients with non-dialysis CKD who use creatine supplementation, with particular attention to health- and sport-related diagnostic pitfalls. The review focuses on creatinine-based eGFR, cystatin C, albuminuria, urinary sediment, biochemical abnormalities, and clinical context. It also proposes a practical, non-validated framework for assessing whether a creatinine increase is more consistent with creatinine-related artefact or true deterioration of kidney function.

2. Methods / literature selection

This article is a narrative review with a clinical interpretation focus. The literature was selected to support discussion of a defined clinical problem: interpretation of kidney function markers in non-dialysis CKD patients using creatine supplementation. The article does not present a systematic review, quantitative synthesis, PRISMA flow diagram, formal risk-of-bias assessment, or meta-analysis. Relevant publications were identified through PubMed, Google Scholar, and current guideline documents. Search terms included: creatine supplementation, creatinine, kidney function, chronic kidney disease, estimated glomerular filtration rate, eGFR, cystatin C, measured GFR, renal biomarkers, and diagnostic pitfall. Terms were used individually and in combination. The last literature search was performed on May 5, 2026. The review prioritized publications from the last 10 years, including systematic reviews, meta-analyses, narrative reviews, clinical guidelines, and articles on kidney function biomarker interpretation. Older sources were considered only when they provided biochemical or methodological information not sufficiently covered by recent literature. Publications were considered relevant when they addressed at least one of the following topics: effects of creatine supplementation on kidney function markers, creatine–creatinine metabolism, limitations of creatinine-based eGFR, cystatin C-based GFR estimation, measured GFR, or interpretation of kidney function in CKD. Sources addressing non-GFR determinants of serum creatinine were considered particularly relevant. The primary population of interest was patients with non-dialysis CKD. This scope was chosen because creatinine-based eGFR, cystatin C-based eGFR, albuminuria, and assessment of CKD progression are most directly applicable before dialysis initiation. Studies involving dialysis or kidney transplant populations were not excluded from background discussion when relevant, but they were not used as the main basis for the proposed interpretation framework.

3. Description of the state of knowledge

3.1. Creatine metabolism and serum creatinine

Creatine is obtained from diet and endogenous synthesis. Most total body creatine is stored in skeletal muscle as free creatine and phosphocreatine. Phosphocreatine acts as a phosphate donor for rapid adenosine triphosphate regeneration during short periods of high energy demand. Creatinine is produced by spontaneous, non-enzymatic conversion of creatine and phosphocreatine [3,4]. The amount of creatinine generated depends partly on the size of the creatine pool and muscle mass [3,7]. Factors increasing creatine availability may therefore increase creatinine generation [3,5,6]. Creatine supplementation may raise serum creatinine through this mechanism without necessarily reducing true GFR [1,5,6]. The clinical problem arises because serum creatinine is used as a kidney function marker despite being influenced by non-filtration factors. Serum creatinine concentration depends on both production and elimination. Reduced GFR increases serum creatinine by reducing renal elimination [7,8]. Creatine supplementation may increase serum creatinine by increasing creatinine generation [3,5,6]. These mechanisms produce the same direction of change in serum creatinine but have different implications for kidney function [7,8]. When creatinine increases due mainly to increased generation, creatinine-based eGFR may appear lower than true filtration [7–9]. This produces a laboratory pattern that may resemble kidney function deterioration [5–7]. In non-dialysis CKD patients, such a pattern may affect disease staging and clinical decisions [7,10].

3.2. Creatinine-based eGFR and its limitations in CKD

Creatinine-based eGFR is widely used in CKD diagnosis, staging, monitoring, drug dosing, and referral decisions [7,8,10]. Its use is supported by availability, low cost, and routine laboratory reporting [8,9]. Its accuracy, however, depends on whether serum creatinine reflects filtration reliably in the assessed patient [7,8]. Creatine supplementation is a non-GFR determinant of serum creatinine [7]. Other determinants include muscle mass, dietary meat intake, high-protein diet, intense physical activity, medications affecting tubular secretion, and acute volume changes [7,8,13]. When these factors change, serum creatinine may change without a proportional change in true GFR [7,8]. Creatinine-based equations interpret a higher serum creatinine value as lower estimated GFR [8,9]. Therefore, a creatine-related rise in serum creatinine may lower eGFRcr even when filtration is stable [5–7]. In non-dialysis CKD patients, this may lead to apparent worsening of GFR category, apparent progression, or changes in medication dosing based on an artefactual estimate [7,9,10]. Creatine supplementation must not become a default explanation for every creatinine rise [7,10]. CKD patients remain susceptible to acute kidney injury, progression of the underlying kidney disease, volume depletion, nephrotoxic medication exposure, urinary obstruction, and exercise-related muscle injury[7,10,12]. A creatinine increase in this population requires assessment beyond supplement history [7,10]. In the proposed interpretation framework, interpretation should depend on whether the creatinine rise is isolated or accompanied by other evidence of kidney dysfunction or kidney damage. Stable cystatin C, stable albuminuria, unchanged urinary sediment, normal potassium and bicarbonate, stable blood pressure, preserved urine output, and absence of acute illness would support creatinine-related artefact [7–9,13]. Parallel worsening of cystatin C-based eGFR, increasing albuminuria, active urinary sediment, hyperkalemia, metabolic acidosis, oliguria, edema, or worsening hypertension would support true kidney function deterioration [7,9,10].

3.3. Evidence on creatine supplementation and kidney function

The relationship between creatine supplementation and kidney function has been evaluated in several reviews and meta-analyses [1,5,6]. Most available studies were conducted in healthy individuals, physically active adults, athletes, or mixed populations without established CKD [1,5]. This limits direct application of the findings to patients with reduced baseline kidney function. A recent systematic review and meta-analysis reported that creatine supplementation was associated with a small increase in serum creatinine, but without a significant difference in GFR compared with control groups [1]. Earlier meta-analytic evidence also did not show evidence of kidney damage during creatine supplementation in the analyzed studies [5]. These findings support the interpretation that creatinine elevation during creatine use may reflect increased creatinine generation rather than reduced filtration in at least some individuals. This evidence should not be interpreted as proof that creatine is safe in every patient with CKD. The available studies were not primarily designed to resolve diagnostic uncertainty in CKD patients using creatine. Many trials relied on serum creatinine or creatinine-based eGFR as kidney function outcomes, which is problematic when the exposure itself may affect creatinine generation [1,5,6]. Few studies used cystatin C, combined creatinine-cystatin C equations, or measured GFR as primary outcomes. Follow-up periods were also often too short to assess long-term CKD progression. A recent narrative review in the *Journal of Education, Health and Sport* discussed common myths and evidence regarding creatine supplementation and renal function[11]. That review emphasized that increased serum creatinine during creatine supplementation does not necessarily indicate kidney damage and that kidney function should not be assessed only by serum creatinine [11]. The present review addresses a narrower question: how this diagnostic issue should be interpreted in patients with established CKD, where creatinine-based changes may affect staging, monitoring, and clinical decisions. The current evidence therefore supports two statements. First, creatine supplementation can increase serum creatinine without confirmed reduction in GFR in some studied populations [1,5,6]. Second, evidence remains insufficient to define a validated diagnostic pathway for CKD patients who use creatine and develop increased serum creatinine. This gap justifies a clinical interpretation framework based on creatine metabolism, limitations of creatinine-based eGFR, cystatin C, albuminuria, urinary sediment, biochemical abnormalities, and clinical context.

3.4. Why CKD is a distinct clinical context

CKD changes the clinical meaning of creatinine variation. In individuals without known kidney disease, a mild increase in serum creatinine during creatine supplementation may raise a question about laboratory interpretation. In patients with established CKD, the same laboratory pattern may influence disease classification, medication dosing, monitoring frequency, referral decisions, and assessment of progression [7,10]. CKD is classified and monitored according to cause, GFR category, and albuminuria category [7] . Creatinine-based eGFR is therefore not only a laboratory value; it is part of the classification system used to describe disease severity and guide clinical decisions [7,10]. If creatine supplementation increases serum creatinine through increased creatinine generation, eGFRcr may decrease even when true filtration is stable. This can create apparent worsening of GFR category without parallel evidence of kidney damage or functional decline. The opposite situation is also relevant. Patients with CKD have reduced renal reserve and higher susceptibility to acute kidney injury from dehydration, infection, nephrotoxic drugs, urinary obstruction, hemodynamic changes, or progression of the underlying kidney disease [7,10,12]. In such patients, creatine use may coexist with true kidney function deterioration. A clinician who attributes a creatinine increase only to supplementation may delay evaluation of acute kidney injury or CKD progression. For this reason, creatine supplementation should be treated as a factor that modifies interpretation of creatinine, not as a diagnosis. The presence of supplementation explains why serum creatinine may be misleading, but it does not determine whether the patient's true kidney function is stable. Interpretation requires comparison between filtration markers, kidney damage markers, biochemical findings, urine findings, and clinical status. This is also consistent with the broader approach to kidney function assessment in CKD. KDIGO emphasizes that serum creatinine may be affected by non-GFR determinants and that cystatin C or measured GFR may be useful when creatinine-based estimates are less reliable [7,10]. In the context of creatine supplementation, this principle has direct clinical relevance. A creatinine rise should be interpreted as a signal requiring contextual assessment rather than as a standalone diagnosis of progression or artefact. Because creatine supplementation may affect serum creatinine without necessarily changing true filtration, interpretation should not rely on a single marker. Table 1 summarizes the main kidney function markers relevant to non-dialysis CKD patients using creatine supplementation, with emphasis on their limitations and clinical interpretation.

Table 1. Kidney function markers during creatine supplementation in patients with non-dialysis CKD: interpretation and limitations

Marker	What it reflects	Potential issue during creatine supplementation	Clinical interpretation in CKD
Serum creatinine	Balance between creatinine generation and renal elimination	May increase because of increased creatinine generation rather than reduced GFR	Should not be interpreted alone as CKD progression
Creatinine-based eGFR	Estimated GFR calculated from serum creatinine	May decrease when serum creatinine rises through non-GFR mechanisms	Apparent eGFRcr decline requires confirmation with other markers
Cystatin C	Alternative filtration marker less directly affected by creatine intake	May be influenced by non-GFR factors such as inflammation, obesity, thyroid disease, corticosteroids, and smoking	Useful when creatinine is suspected to be unreliable, but not an ideal marker
Combined creatinine cystatin C eGFR	GFR estimate integrating two filtration markers with different non-GFR determinants	Still an estimate, not a direct measurement of GFR	May improve interpretation when creatinine and cystatin C are discordant

Albuminuria / ACR	Marker of kidney damage, especially glomerular injury	Creatine intake alone should not explain new or increasing albuminuria	Increasing ACR supports true kidney damage or progression rather than isolated creatinine artefact
Urinary sediment	Evidence of active urinary tract or kidney pathology	Creatine intake should not produce active sediment	Hematuria, casts, or new sediment abnormalities require evaluation beyond supplementation
Serum potassium	Renal excretory function and medication/AKI effects	Not directly increased by creatine supplementation	Hyperkalemia supports clinically relevant kidney dysfunction or medication-related risk
Serum bicarbonate	Acid-base regulation	Not directly lowered by creatine supplementation	Metabolic acidosis supports clinically relevant kidney dysfunction
Measured GFR	Direct or reference-standard assessment of filtration, depending on method used	Not dependent on serum creatinine generation	Most useful when eGFR results are discordant and clinical decisions depend on accurate GFR

Based on current CKD guideline recommendations, GFR estimation literature, cystatin C literature, and reviews on creatine supplementation and kidney function [1,3,5–9,12,13].

4. Diagnostic pitfalls in non-dialysis CKD patients using creatine

Creatine supplementation may alter the interpretation of kidney function markers in CKD through two opposite diagnostic errors. The first error is overdiagnosis of kidney function deterioration when a creatinine rise is caused mainly by increased creatinine generation. The second error is underdiagnosis of true kidney injury when a creatinine rise is attributed too quickly to supplementation. Both errors are clinically relevant because CKD monitoring relies on serial interpretation of eGFR, albuminuria, urine findings, biochemical abnormalities, and clinical status [7,10].

4.1. Assuming that increased creatinine equals kidney function deterioration

A rise in serum creatinine is often interpreted as reduced kidney filtration. This interpretation is appropriate when creatinine generation is stable and the main variable affecting serum creatinine is renal elimination. During creatine supplementation, this assumption may be less reliable because creatine intake may increase the amount of creatinine generated from creatine and phosphocreatine [3,5,6]. In this setting, serum creatinine may increase without a parallel decline in true GFR. The laboratory pattern may therefore resemble kidney function deterioration even when filtration is stable. This is especially relevant in CKD, where a small absolute change in serum creatinine may produce a clinically meaningful change in eGFRcr category or progression assessment [7,10]. This does not mean that creatinine becomes useless. It means that creatinine must be interpreted as a marker influenced by both production and elimination. In a CKD patient using creatine, a creatinine rise should prompt assessment of timing, dose, baseline kidney function, cystatin C, albuminuria, urinary sediment, biochemical abnormalities, and clinical status rather than immediate classification as CKD progression.

4.2. Interpreting eGFRcr decline as CKD progression

Creatinine-based eGFR equations use serum creatinine as a central input. If serum creatinine rises, eGFRcr decreases according to the equation used [8,9]. When the creatinine rise is caused mainly by increased generation rather than reduced filtration, the resulting eGFRcr decline may be apparent rather than functional. This pitfall is clinically important because CKD staging and monitoring rely strongly on GFR categories [7,10]. A patient using creatine may appear to move to a lower eGFR category despite stable cystatin C, stable albuminuria, unchanged urinary sediment, and no clinical evidence of kidney deterioration. In such a case, the change in eGFRcr should be interpreted as uncertain until supported or contradicted by additional markers. A decline in eGFRcr should be treated more seriously when it is accompanied by changes that are not explained by creatine-related creatinine generation. These include rising cystatin C, falling eGFRcys or eGFRcr-cys, increasing albuminuria, active urinary sediment, hyperkalemia, metabolic acidosis, oliguria, edema, or worsening hypertension [7–9,13].

4.3. Attributing true kidney injury to creatine supplementation

The opposite error may be more dangerous. A clinician may identify creatine supplementation and assume that a creatinine increase is benign. This creates the risk of missing acute kidney injury, progression of underlying CKD, obstructive uropathy, volume depletion, medication-related nephrotoxicity, or hemodynamic deterioration [7,10]. Creatine supplementation should therefore be treated as a modifier of creatinine interpretation, not as an explanation that ends diagnostic assessment. CKD patients remain vulnerable to kidney function decline from common triggers, including dehydration, infection, non-steroidal anti-inflammatory drugs, iodinated contrast, renin-angiotensin system blockers or SGLT2 inhibitors during acute illness, urinary obstruction, and progression of the primary kidney disease [7,10,12]. A creatinine rise should not be attributed primarily to supplementation when there are clinical or laboratory features suggesting true kidney dysfunction. These include reduced urine output, fluid overload, new or worsening hypertension, hyperkalemia, metabolic acidosis, rising cystatin C, increasing albuminuria, new proteinuria, or active urinary sediment [7,10]

4.4. Ignoring exercise-related muscle injury and rhabdomyolysis

Creatine users are often physically active. Physical activity, including aerobic and resistance exercise, is recommended for clinically stable patients with non-dialysis CKD, and some patients may already participate in regular or vigorous exercise programs [14]. Heavy exercise, muscle injury, and exertional rhabdomyolysis may increase serum creatinine and creatine kinase and may also cause true acute kidney injury [15,16]. This creates a separate diagnostic problem. A creatinine increase after intense training may not be caused only by creatine supplementation; it may reflect muscle breakdown, volume depletion, pigment-associated kidney injury, or a combination of these mechanisms [15,16]. Clinical features suggesting exercise-related muscle injury include severe muscle pain, muscle swelling, weakness, dark urine, markedly elevated creatine kinase, myoglobinuria, electrolyte abnormalities, or acute kidney injury after strenuous exercise [15,16]. In such cases, attributing creatinine elevation to creatine supplementation alone would be unsafe. In CKD patients, this issue has greater clinical significance because reduced renal reserve may increase vulnerability to acute kidney injury and may reduce tolerance for additional renal stressors [7,10]. When creatinine rises in a CKD patient using creatine and performing intense exercise, interpretation should include recent training load, hydration status, muscle symptoms, urine color, creatine kinase, electrolytes, urinalysis, cystatin C, and albuminuria [7,10,14–16]. Creatine supplementation is only one part of the exposure history and should not replace assessment for exercise-related kidney injury.

4.5. Treating cystatin C as a perfect confirmatory test

Cystatin C is useful when creatinine is suspected to be affected by non-GFR determinants, including creatine intake. A stable cystatin C-based eGFR during a creatinine-based eGFR decline may support the possibility of creatinine-related artefact [7,8,13]. Combined creatinine-cystatin C equations may also improve GFR estimation when one marker is less reliable [9]. Cystatin C is not a perfect marker. Its concentration may be influenced by factors other than GFR, including inflammation, obesity, thyroid dysfunction, smoking, and corticosteroid use [12,13]. Therefore, cystatin C should be interpreted together with albuminuria, urinary sediment, electrolytes, acid-base status, blood pressure, volume status, and the clinical course. Discordance between eGFRcr and eGFRcys should not be ignored. In a CKD patient using creatine, lower eGFRcr with stable eGFRcys may suggest creatinine-related artefact. Parallel decline in both eGFRcr and eGFRcys should increase concern for true reduction in filtration. When the result will influence an important clinical decision and estimated markers remain discordant, measured GFR may be required [7,8].

5. Clinical interpretation framework

The proposed framework is intended to organize clinical reasoning in non-dialysis CKD patients who use creatine supplementation and develop increased serum creatinine or decreased eGFRcr. It should not be interpreted as a validated diagnostic algorithm. Its purpose is to reduce premature classification of the finding as either CKD progression or benign creatinine-related artefact.

5.1. Confirm creatine exposure

The first step is to confirm whether the patient is using creatine and to characterize the exposure. The assessment should include the form of creatine, daily dose, duration of use, recent dose escalation, loading phase, timing of the last dose before blood sampling, concurrent high-protein diet, resistance training, endurance exercise, and other supplements. This step matters because creatinine interpretation depends on the clinical context in which the blood sample was obtained. A recent loading phase, increased training intensity, high meat intake, dehydration, or acute illness may all influence serum creatinine or kidney function markers through different mechanisms [7,8,14–16]. Creatine use alone should not be treated as sufficient explanation for a creatinine rise.

5.2. Assess the temporal relationship

The timing of the creatinine change should be compared with the start of supplementation, change in dose, loading phase, training changes, acute illness, medication changes, and previous kidney function results. A creatinine increase that appears shortly after creatine initiation or dose escalation may support creatinine-related artefact, especially if other kidney markers remain stable [1,5,6]. The temporal relationship is supportive, not diagnostic. A creatinine rise after starting creatine may still represent acute kidney injury, progression of CKD, volume depletion, drug-related nephrotoxicity, or exercise-related muscle injury. Conversely, a creatinine rise unrelated to creatine timing should not be attributed to supplementation without additional evidence.

5.3. Compare creatinine-based and cystatin C-based filtration markers

When creatinine-based eGFR decreases in a CKD patient using creatine, cystatin C may help assess whether the change is limited to creatinine-based estimation. A stable cystatin C or stable eGFRcys during a decline in eGFRcr supports the possibility that creatinine has increased through non-GFR mechanisms [7,8,13]. Combined creatinine-cystatin C equations may improve interpretation because they integrate two filtration markers with different non-GFR determinants [9]. Evidence that creatine intake is not associated with elevated circulating cystatin C further supports the use of cystatin C as a complementary marker when serum creatinine is difficult to interpret during creatine exposure [17]. However, this should not be interpreted as proof that cystatin C is unaffected by all relevant clinical conditions, because cystatin C also has non-GFR determinants. Parallel worsening of eGFRcr and eGFRcys should increase concern for true decline in filtration. This pattern is not explained by creatine-related creatinine generation alone. Cystatin C should still be interpreted cautiously because inflammation, obesity, thyroid dysfunction, corticosteroid exposure, smoking, and other non-GFR determinants may influence its concentration [12,13].

5.4. Evaluate kidney damage markers

Creatinine and eGFR describe filtration but do not fully describe kidney damage. In CKD patients using creatine, interpretation should include albuminuria, proteinuria, and urinary sediment [7,10]. Stable albuminuria and unchanged urinary sediment support the possibility that an isolated creatinine rise is not accompanied by new kidney damage. New or increasing albuminuria, increasing proteinuria, hematuria, casts, or active urinary sediment should shift interpretation toward true kidney disease activity, CKD progression, or superimposed acute kidney injury. Creatine-related creatinine generation does not explain new albuminuria or active urinary sediment. These findings require diagnostic evaluation according to the suspected kidney disease process [7,10].

5.5. Assess biochemical and clinical context

The interpretation should include markers of kidney function beyond creatinine. Potassium, bicarbonate, urea, acid-base status, blood pressure, volume status, urine output, and symptoms of acute illness should be reviewed [7,10]. Stable electrolytes, stable bicarbonate, preserved urine output, stable blood pressure, and absence of edema or acute illness support creatinine-related artefact. Hyperkalemia, metabolic acidosis, oliguria, edema, new or worsening hypertension, rising urea, hypotension, sepsis, vomiting, diarrhea, or dehydration support true kidney dysfunction or acute kidney injury. Medication history should also be reviewed, including non-steroidal anti-inflammatory drugs, iodinated contrast, aminoglycosides, diuretics, renin-angiotensin system blockers, SGLT2 inhibitors during acute illness, and other nephrotoxic or hemodynamically active drugs [7,10].

5.6. Consider exercise-related muscle injury

Recent intense exercise should be assessed separately from creatine supplementation. Muscle injury may increase serum creatinine and creatine kinase and may also cause acute kidney injury through rhabdomyolysis [15,16]. This is relevant because creatine users often perform resistance training or endurance exercise. Symptoms such as severe muscle pain, swelling, weakness, dark urine, reduced urine output, or marked fatigue should prompt evaluation for muscle injury. Creatine kinase, electrolytes, urinalysis, urine color, hydration status, and recent training load should be assessed when clinically indicated [15,16]. In this setting, attributing creatinine elevation only to creatine supplementation may miss a clinically important cause of kidney injury.

5.7. Consider temporary discontinuation and retesting

If the patient is clinically stable and there are no red flags for acute kidney injury or CKD progression, temporary discontinuation of creatine followed by repeat testing may help interpretation. Retesting should ideally occur under comparable conditions, with attention to hydration, diet, recent exercise, and medication changes. A fall in serum creatinine after stopping creatine, with stable cystatin C, stable albuminuria, unchanged urinary sediment, and stable clinical status, supports creatinine-related artefact. Persistent creatinine elevation, progressive rise in creatinine, worsening cystatin C-based eGFR, increasing albuminuria, active urinary sediment, electrolyte abnormalities, or clinical deterioration should prompt evaluation for true kidney function decline.

5.8. Use measured GFR when clinical decisions require higher accuracy

Estimated GFR may be insufficient when creatinine-based and cystatin C-based results are discordant and the result will influence an important decision. Such decisions may include drug dosing with narrow therapeutic index medications, assessment of CKD progression, eligibility for specific therapies, or nephrology decisions based on GFR thresholds. In these situations, measured GFR may be appropriate if available [7,8]. Measured GFR is not affected by creatinine generation and can help resolve uncertainty when serum creatinine is suspected to be unreliable. Its use should be reserved for situations where the expected clinical benefit justifies the additional complexity, cost, and availability limitations.

5.9. Summary of the proposed framework

The proposed framework is based on pattern recognition rather than a single diagnostic marker. A creatinine rise in a CKD patient using creatine is more consistent with creatinine-related artefact when it is temporally related to supplementation, isolated to creatinine-based measures, accompanied by stable cystatin C-based eGFR, stable albuminuria, unchanged urinary sediment, stable electrolytes, stable acid-base status, and stable clinical condition. True kidney function deterioration becomes more likely when creatinine rise is progressive, persists after stopping creatine, or occurs together with worsening cystatin C-based eGFR, increasing albuminuria, active urinary sediment, hyperkalemia, metabolic acidosis, oliguria, edema, worsening hypertension, acute illness, nephrotoxic exposure, or evidence of muscle injury. The proposed framework should not replace clinical judgment. It provides a structured approach to avoid two errors: misclassifying creatine-related creatinine elevation as CKD progression and dismissing true kidney deterioration as a supplementation-related artefact. Table 2 summarizes the main clinical, biochemical, and laboratory patterns that may support either creatinine-related artefact or true kidney function deterioration in patients with non-dialysis CKD using creatine supplementation.

Table 2. Differentiating creatine-related creatinine elevation from true kidney function deterioration in patients with non-dialysis CKD

Assessment domain	More consistent with creatinine-related artefact	More consistent with true kidney function deterioration
Temporal relationship	Creatinine rises after starting creatine, increasing dose, or loading phase	Creatinine rises independently of supplementation or continues to rise after stopping creatine
Serum creatinine	Mild increase without other abnormalities	Progressive or large increase, especially with other abnormal findings
Creatinine-based eGFR	Apparent decline isolated to eGFRcr	Decline accompanied by other markers of reduced filtration or kidney damage
Cystatin C / eGFRcys	Stable cystatin C and stable eGFRcys	Rising cystatin C or falling eGFRcys
Combined eGFRcr-cys	Stable or closer to previous baseline than eGFRcr	Declines in parallel with eGFRcr and eGFRcys
Albuminuria / ACR	Stable compared with baseline	New or increasing albuminuria
Proteinuria	Stable compared with baseline	New or increasing proteinuria
Urinary sediment	No new abnormalities	Hematuria, casts, or active sediment

Potassium	Stable	Hyperkalemia, especially if new or worsening
Bicarbonate / acid-base status	Stable bicarbonate	Metabolic acidosis or falling bicarbonate
Blood pressure	Stable	New or worsening hypertension
Volume status	No edema, no signs of fluid overload	Edema, fluid overload, pulmonary congestion
Urine output	Preserved urine output	Oliguria or marked reduction in urine output
Acute illness	No dehydration, infection, vomiting, diarrhea, or hemodynamic instability	Acute illness, volume depletion, sepsis, or hypotension
Nephrotoxic exposure	No NSAIDs, contrast exposure, aminoglycosides, or other nephrotoxins	Recent nephrotoxic exposure or medication change
Exercise-related muscle injury	No severe muscle pain, dark urine, or marked CK elevation	CK elevation, myalgia, dark urine, or suspected rhabdomyolysis
Response to temporary discontinuation	Creatinine decreases after stopping creatine while other markers remain stable	Creatinine remains elevated or worsens after stopping creatine
Measured GFR	Stable measured GFR if performed	Reduced measured GFR if performed

Note: This table represents a proposed clinical interpretation framework based on indirect evidence, CKD guideline recommendations, literature on creatinine- and cystatin C-based GFR estimation, reviews of creatine supplementation and renal function, and literature on exertional rhabdomyolysis and AKI; it has not been prospectively validated [1,3,5–16].

6. Clinical implications

The interpretation of serum creatinine in patients with non-dialysis CKD should include supplement history. Creatine use is often not recorded in medication lists, because patients may not consider it a clinically relevant exposure. Direct questioning about creatine, protein supplements, pre-workout products, high-protein diet, recent resistance training, and endurance exercise can prevent incorrect interpretation of kidney function markers [2,7,14–16].

6.1. Implications for clinical history-taking

Patients with non-dialysis CKD should be asked about creatine supplementation when serum creatinine increases or eGFRcr decreases without an obvious explanation. The history should include dose, formulation, duration of use, recent loading phase, timing of the last dose, changes in training intensity, hydration status, dietary protein intake, and use of other supplements. This information should be collected before classifying the result as CKD progression. It should also be collected before dismissing the result as a supplement-related artefact. In this setting, creatine exposure is one variable in the interpretation of creatinine, not a final diagnosis.

6.2. Implications for laboratory interpretation

A creatinine increase in a patient with non-dialysis CKD using creatine should be interpreted together with other markers. Creatinine-based eGFR may be misleading when creatinine generation changes, because the equation cannot distinguish increased creatinine production from reduced filtration [7–9]. When available, cystatin C-based eGFR or combined creatinine-cystatin C eGFR may help clarify discordant findings [7–9,13]. Stable eGFRcys or eGFRcr-cys during an isolated eGFRcr decline may support creatinine-related artefact. Worsening eGFRcys or eGFRcr-cys should increase concern for true reduction in filtration. Case-based literature also illustrates that cystatin C may clarify situations in which creatinine-based eGFR suggests kidney dysfunction that is inconsistent with the clinical picture [18]. However, such evidence should be interpreted as illustrative rather than definitive, and it should not replace guideline-based assessment or clinical judgment. Laboratory interpretation should also include albuminuria, proteinuria, urinary sediment, potassium, bicarbonate, urea, and clinical status. New albuminuria, active sediment, hyperkalemia, metabolic acidosis, oliguria, edema, or worsening hypertension should not be explained by creatine-related creatinine generation alone [7,10]. Although cystatin C is useful when creatinine-based estimates are suspected to be unreliable, real-world implementation of cystatin C testing remains variable, which may limit its routine use in some clinical settings [19].

6.3. Implications for CKD monitoring and medication dosing

In non-dialysis CKD, eGFR categories influence monitoring intervals, medication dosing, referral decisions, and assessment of progression [7,10]. A creatine-related decrease in eGFRcr may therefore lead to unnecessary concern, additional diagnostic testing, or inappropriate medication changes if interpreted without context. The opposite error also has clinical consequences. If true kidney function decline is attributed to creatine supplementation without further assessment, diagnosis of acute kidney injury or CKD progression may be delayed. This is relevant in patients exposed to dehydration, infection, non-steroidal anti-inflammatory drugs, contrast agents, hemodynamic medication effects, urinary obstruction, or intense exercise [7,10,14–16]. When kidney function estimates influence high-risk decisions, such as dosing of drugs with a narrow therapeutic index, eligibility for treatment, or classification of clinically relevant CKD progression, reliance on eGFRcr alone may be insufficient. In such cases, eGFRcr-cys or measured GFR should be considered if available [7–9].

6.4. Implications for patient counselling

Patients with non-dialysis CKD who use or consider using creatine should be advised to report supplementation to their physician. They should also be informed that creatine may complicate interpretation of serum creatinine and eGFRcr. This counselling should not be framed as automatic prohibition or automatic reassurance. A practical message is that creatine use may change laboratory interpretation and should be disclosed before kidney function testing. Patients should also be advised to avoid blood testing immediately after unusually intense exercise, dehydration, acute illness, or major dietary changes when possible, because these factors may further complicate interpretation [7,8,14–16]. If creatinine rises during supplementation, patients should not independently stop or continue creatine without clinical assessment. The appropriate response depends on the full pattern of results: cystatin C, albuminuria, urinary sediment, electrolytes, acid-base status, blood pressure, symptoms, training history, medication exposure, and baseline kidney function.

6.5. Implications for clinicians interpreting creatine-related creatinine changes

Clinicians should avoid two reflexive interpretations. The first is assuming that increased creatinine equals CKD progression. The second is assuming that creatine explains every creatinine increase. The safer approach is to treat the result as an interpretation problem requiring comparison of multiple markers. In a clinically stable patient with non-dialysis CKD, isolated creatinine rise after creatine initiation, stable cystatin C-based eGFR, stable albuminuria, unchanged urinary sediment, and no biochemical or clinical evidence of kidney dysfunction support creatinine-related artefact. In a patient with parallel worsening of cystatin C-based eGFR, increasing albuminuria, active urinary sediment, hyperkalemia, metabolic acidosis, oliguria, edema, acute illness, nephrotoxic exposure, or evidence of muscle injury, true kidney function deterioration should be evaluated.

7. Evidence gaps and future research

Direct evidence for creatine supplementation in patients with non-dialysis CKD is limited. Most data on creatine and kidney function come from healthy individuals, physically active adults, athletes, or mixed populations without established CKD [1,5,6]. These studies are useful for understanding the relationship between creatine supplementation, serum creatinine, and GFR markers, but they cannot define diagnostic interpretation or long-term safety in patients with reduced baseline kidney function. A major evidence gap concerns the lack of prospective studies designed specifically for patients with non-dialysis CKD who use creatine. Future studies should include clearly defined CKD stages, baseline albuminuria, cause of CKD, medication exposure, dietary protein intake, physical activity level, and creatine dose. Without these details, it remains difficult to determine whether creatinine changes reflect supplementation, kidney function decline, exercise-related muscle injury, or other clinical factors. Another gap concerns outcome measurement. Many creatine studies use serum creatinine or creatinine-based eGFR as renal outcomes [1,5]. This is problematic when the intervention may influence creatinine generation. Future trials in non-dialysis CKD should include cystatin C, combined creatinine-cystatin C eGFR, albuminuria, urinary sediment, electrolytes, acid-base status, and, where feasible, measured GFR. Such designs would better distinguish changes in creatinine generation from changes in true filtration. Long-term safety also remains insufficiently defined. Short follow-up may miss clinically relevant CKD progression, delayed adverse effects, or interactions with acute illness, nephrotoxic exposure, or dehydration. Future studies should assess not only changes in serum creatinine, but also CKD progression, albuminuria progression, acute kidney injury episodes, hospitalization, adverse events, and discontinuation rates. Patients with different CKD etiologies may not have the same risk profile. Diabetic kidney disease, hypertensive nephrosclerosis, glomerular disease, tubulointerstitial disease, hereditary kidney disorders, and solitary kidney may differ in susceptibility to hemodynamic stress, proteinuria progression, acute kidney injury, or medication-related complications. Future research should avoid treating non-dialysis CKD as one homogeneous population. The role of physical activity requires separate investigation. Exercise is recommended for clinically stable patients with non-dialysis CKD, but intense exercise may also affect serum creatinine, creatine kinase, hydration status, and risk of exertional rhabdomyolysis [14–16]. Studies evaluating creatine in non-dialysis CKD should therefore record training type, intensity, timing relative to blood sampling, muscle symptoms, creatine kinase, and hydration status. Evidence from dialysis populations should be interpreted separately. Creatine supplementation has been studied in hemodialysis patients, but those data should not be directly extrapolated to the proposed framework for non-dialysis CKD, because serum creatinine, eGFR, and assessment of CKD progression have different clinical roles after dialysis initiation [20]. Dialysis populations may require separate frameworks focused on muscle mass, nutritional status, inflammation, functional capacity, and dialysis-specific outcomes. Future research should also evaluate whether a practical interpretation framework can be prospectively tested. A study could compare creatinine, cystatin C, combined eGFRcr-cys, albuminuria, urinary sediment, and measured GFR before and after creatine supplementation in clinically stable non-dialysis CKD patients. Such a design would allow assessment of whether isolated creatinine increases can be reliably separated from true kidney function deterioration. Until such studies are available, interpretation must rely on indirect evidence, guideline-based principles, and clinical pattern recognition. This limitation should be acknowledged explicitly when applying the proposed framework in practice.

8. Limitations

This review has several limitations. First, it is a narrative review, not a systematic review. The literature was selected to support a clinically focused discussion, and no formal risk-of-bias assessment, PRISMA flow diagram, or quantitative synthesis was performed. The conclusions should therefore be interpreted as a structured clinical interpretation, not as a pooled estimate of effect. Second, direct evidence regarding creatine supplementation in patients with non-dialysis CKD is limited. Much of the available evidence on creatine and kidney function comes from healthy individuals, physically active adults, athletes, or mixed populations without established CKD [1,5,6]. These data are useful for understanding creatine-related changes in serum creatinine, but they cannot be directly extrapolated to patients with reduced baseline kidney function. Third, the proposed framework is based on indirect evidence, CKD guideline recommendations, biomarker literature, and clinical reasoning. It has not been prospectively validated. The framework should therefore be used as an aid to interpretation, not as a diagnostic rule. Fourth, serum creatinine and cystatin C both have non-GFR determinants. Although cystatin C may be useful when creatinine is affected by creatine intake, cystatin C may also be influenced by factors such as inflammation, obesity, thyroid dysfunction, corticosteroid exposure, and smoking [12,13]. Discordance between eGFRcr and eGFRcys therefore requires interpretation in clinical context. Fifth, dialysis and kidney transplant populations were not the main target of the proposed framework. Evidence from hemodialysis studies was considered only as contextual evidence, because serum creatinine, eGFR, and assessment of CKD progression have different clinical roles after dialysis initiation [20]. Separate interpretive frameworks may be required for dialysis and transplant populations. Finally, the proposed approach does not replace clinical judgment. In patients with non-dialysis CKD, increased serum creatinine during creatine supplementation may represent creatinine-related artefact, true kidney function deterioration, acute kidney injury, exercise-related muscle injury, medication effects, volume depletion, or a combination of these factors. Clinical decisions should be based on the full pattern of laboratory, urinary, biochemical, and clinical findings.

9. Conclusions

Creatine supplementation may complicate interpretation of kidney function markers in patients with non-dialysis CKD. The main diagnostic issue is not limited to potential nephrotoxicity. The more specific problem is that creatine may increase serum creatinine through increased creatinine generation, which can lead to an apparent decrease in creatinine-based eGFR without a confirmed reduction in true GFR.

This interpretation is clinically relevant because creatinine-based eGFR remains central to CKD staging, monitoring, medication dosing, referral decisions, and assessment of progression before dialysis initiation. In this setting, an isolated rise in serum creatinine should not be automatically classified as CKD progression. It should also not be dismissed as benign without further assessment. A multi-marker approach may reduce the risk of diagnostic error. Stable cystatin C-based eGFR, stable combined creatinine-cystatin C eGFR, stable albuminuria, unchanged urinary sediment, normal potassium and bicarbonate, stable blood pressure, preserved urine output, and absence of acute illness support creatinine-related artefact. Parallel worsening of cystatin C-based eGFR, increasing albuminuria or proteinuria, active urinary sediment, hyperkalemia, metabolic acidosis, oliguria, edema, worsening hypertension, nephrotoxic exposure, or evidence of muscle injury should prompt evaluation for true kidney function deterioration. The proposed framework should be regarded as a clinical interpretation tool rather than a validated diagnostic algorithm. Further prospective studies in patients with non-dialysis CKD are needed to assess creatine-related changes in serum creatinine alongside cystatin C, albuminuria, urinary sediment, biochemical parameters, clinical outcomes, and measured GFR.

10. Disclosure section

Author
Contributions
Conceptualization, M.Ch.

Methodology, M.Ch.

Literature search, M.Ch., A.C. and M.S.

Data analysis and synthesis, M.Ch., A.C. and B.K.

Writing—original draft preparation, M.Ch., A.C., M.Maj and M.N.

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The authors declare no conflict of interest.

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